7-5-2016

Impact of engineered nanoparticles in initiating or modulating pathology-related Inflammation

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CONSIGLIO NAZIONALE DELLE RICERCHE

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Role of macrophages in driving and regulating inflammation

Safety and exploitation of the interaction with nanomaterials

Diana Boraschi

Hernstein, July 5, 2016

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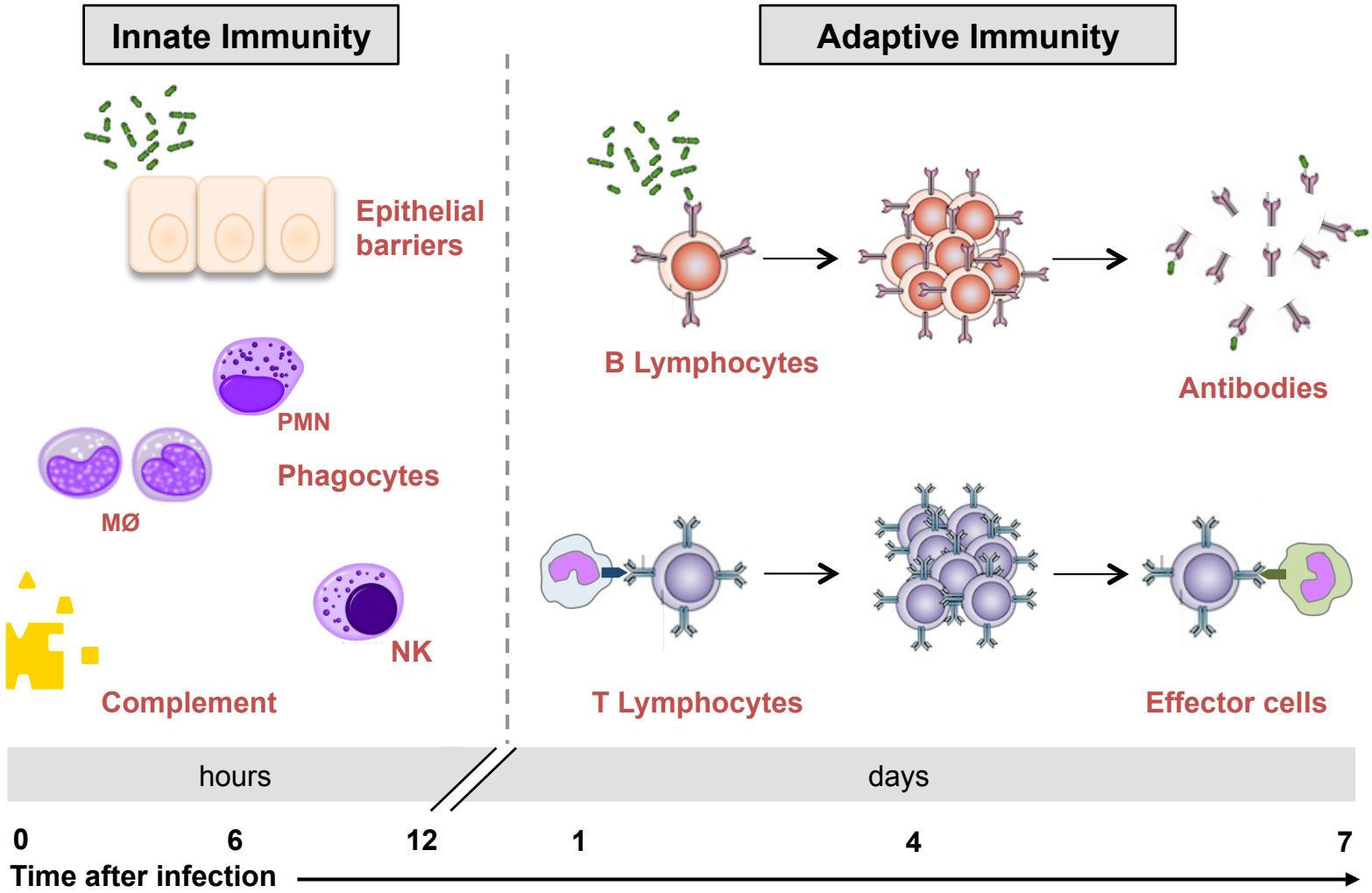
Immune System



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Nanoparticle interaction with immune system

Where do they go when inoculated *in vivo*?

- large part goes undetected and is rapidly excreted
- uptake by inflamed tissues is facilitated by vascular leakage
- targeting molecules may direct them to selected tissues
- **significant amount is taken up by leukocytes**

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Nanomedicines and the immune system

- **Nanodrug, delivery and imaging systems**

  Must persist in the blood and diffuse into tissues long enough for effect

  - How to deal with the immune surveillance, in particular by blood/tissue phagocytes
  - How to limit unwanted immune stimulation (*e.g.*, complement activation)

- **Adjuvants and immunomodulators**

  Must deliver molecules/signals to immune cells

  - How to specifically target the objective
  - How to reduce unwanted effects on immune functions

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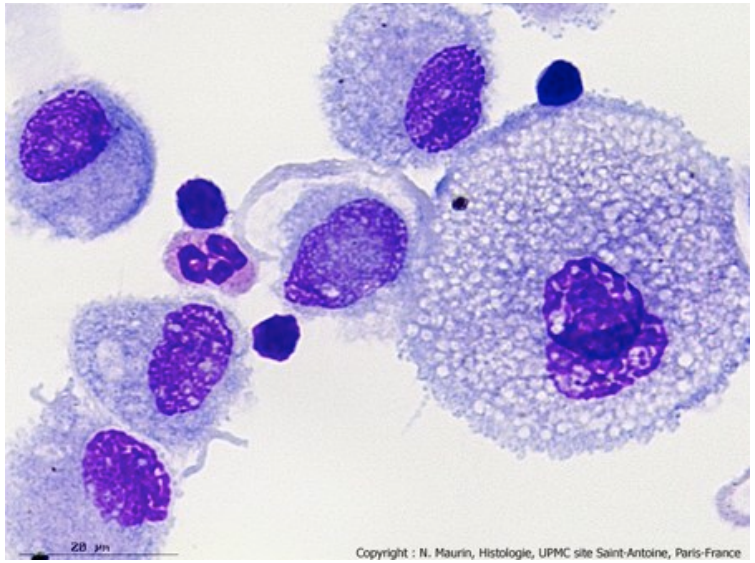
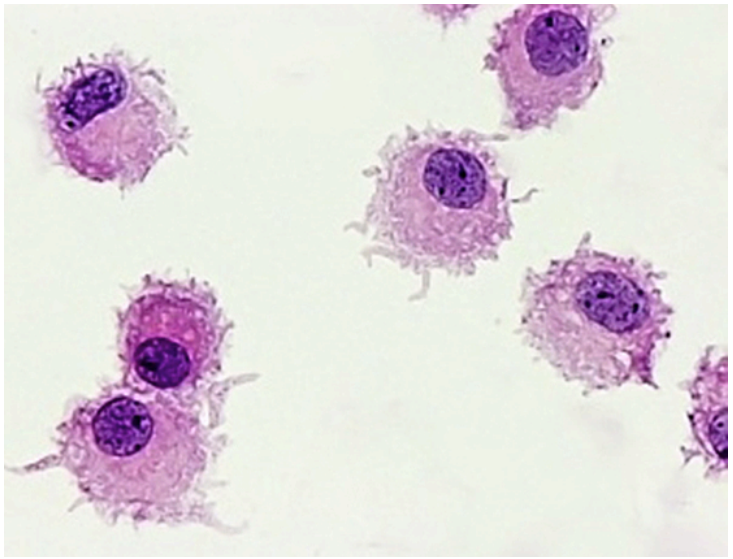
How a nanovaccine can achieve protective immunity

- NPs can favour antigen uptake by phagocytes (the antigen-presenting cells)

Macrophages



Dendritic cells



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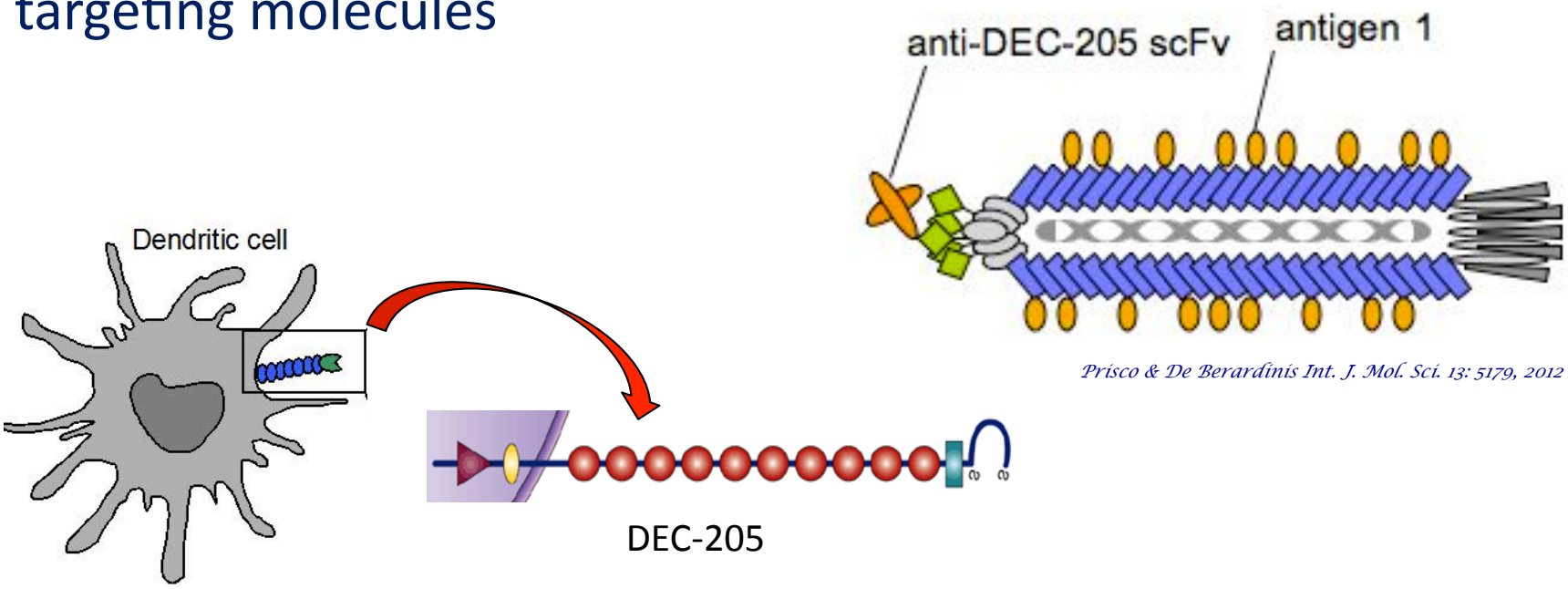
How a nanovaccine can achieve protective immunity

- NPs can be engineered to carry the antigenic cargo and targeting molecules

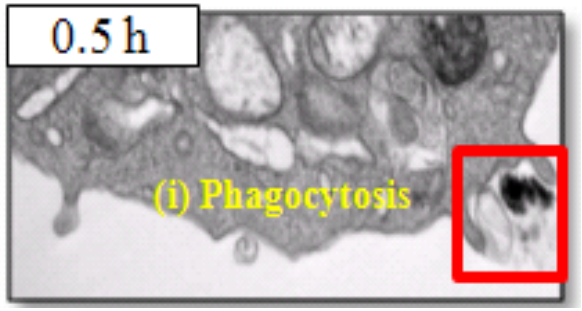


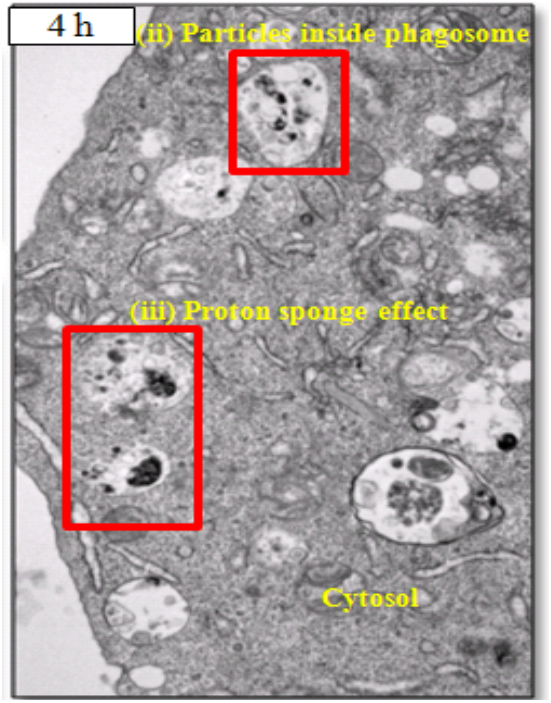
Prisco & De Berardinis Int. J. Mol. Sci. 13: 5179, 2012

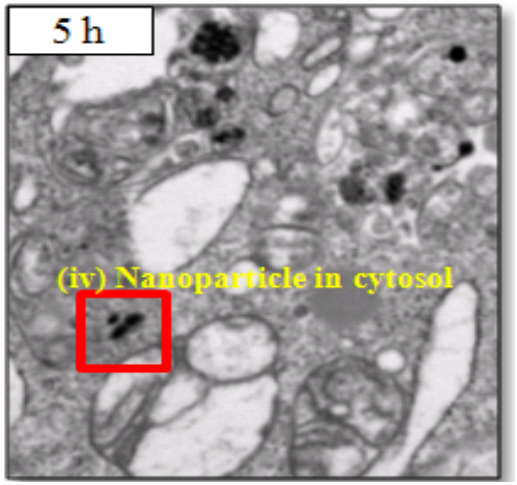
CONSIGLIO NAZIONALE DELLE RICERCHE

How a nanovaccine can achieve protective immunity

- NPs can be engineered to achieve cross-presentation, leading to induction of both cytotoxic T cells and antibody production







Firdous et al. Acta Biomaterialia 10: 4606, 2014

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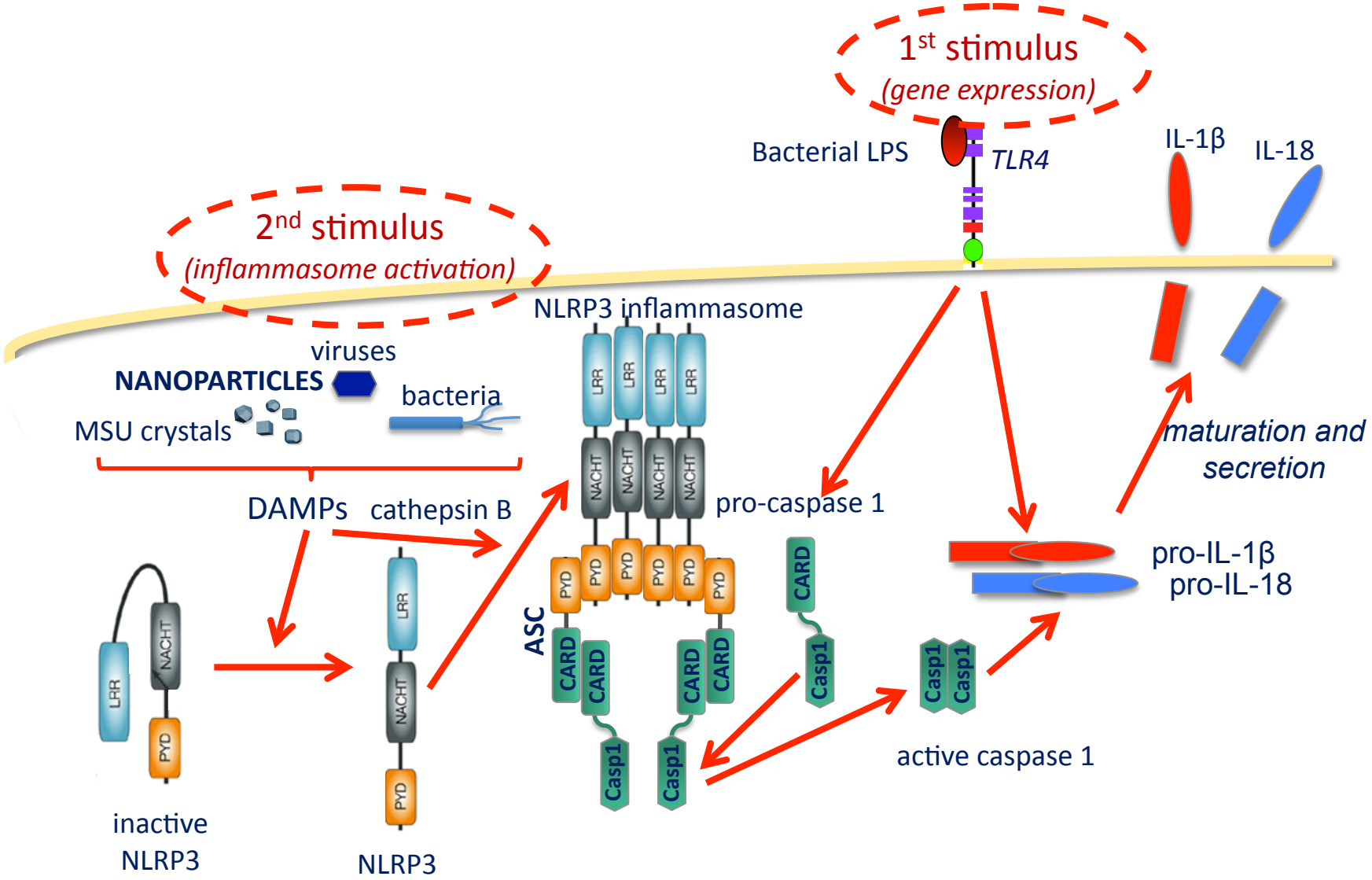
NPs can act as adjuvants by activating the NLRP3 inflammasome



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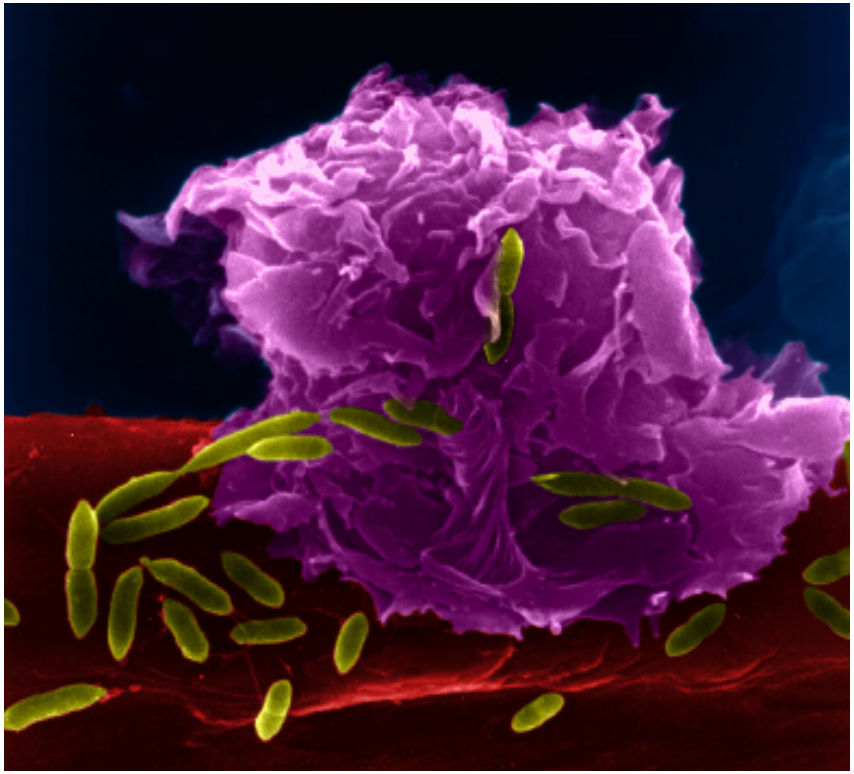
Assessing the immunosafety of nanoparticles

- Need of reliable and valid models
  - Ability to induce pathological inflammation
  - Ability to interfere with physiological inflammation

CONSIGLIO NAZIONALE DELLE RICERCHE

Mononuclear phagocytes



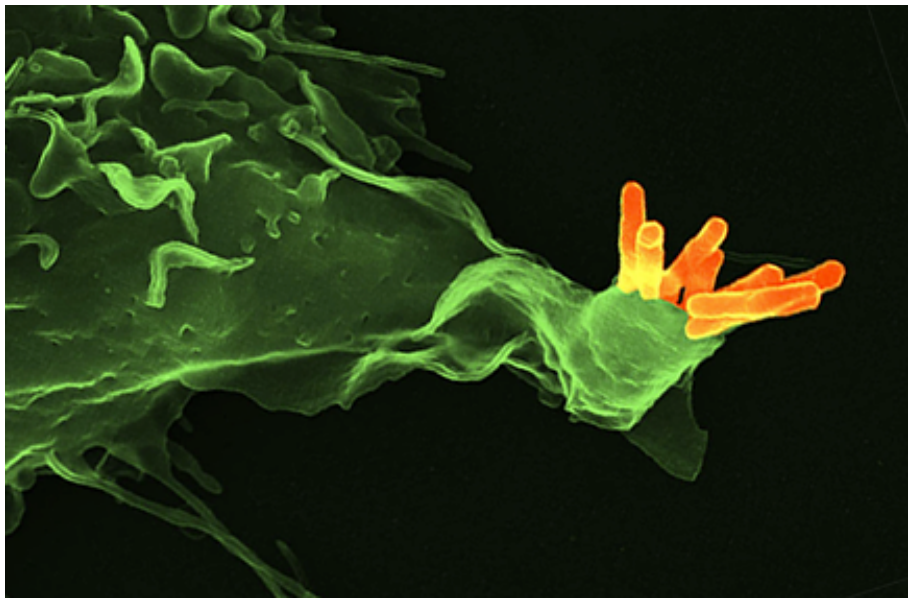


Photo: Volker Brinkmann, MPIIB Berlin

Photo: Dennis Kunkel Microscopy, Inc.

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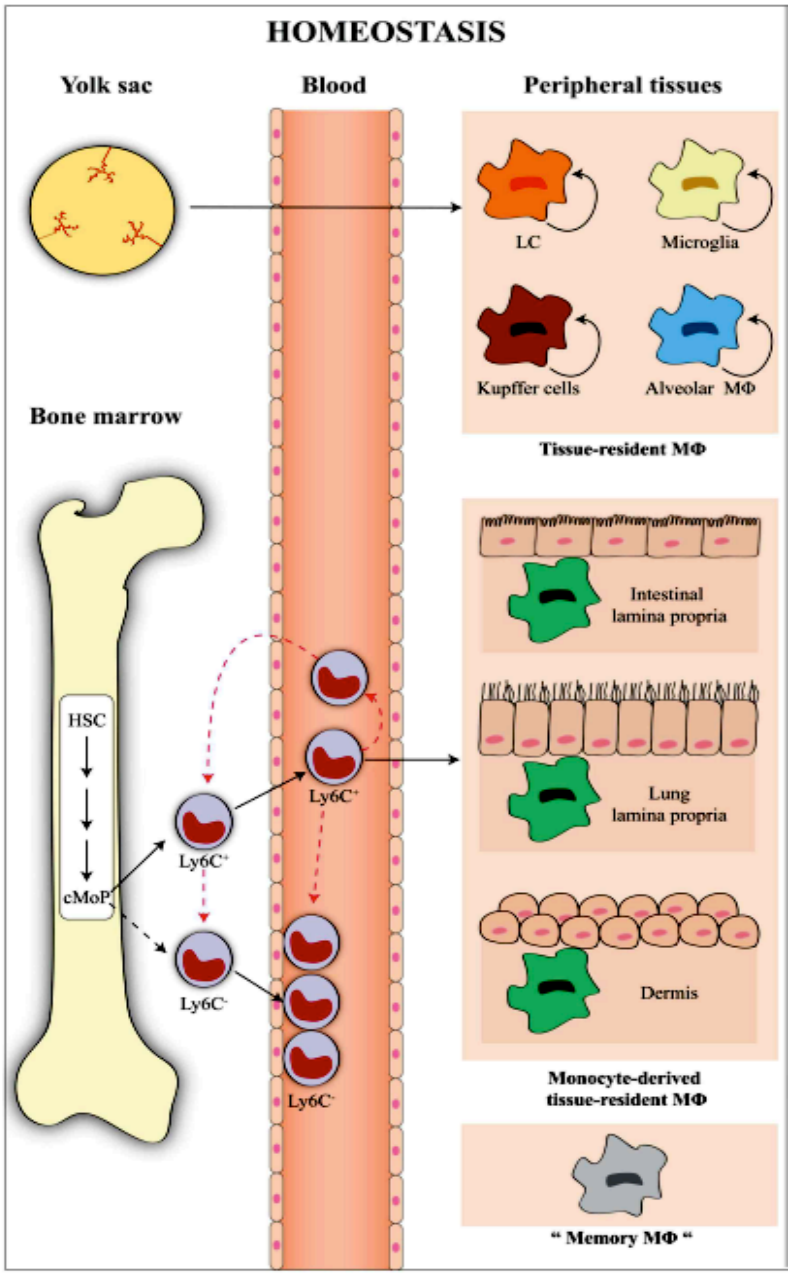
Monocytes and macrophages



Italiani & Boraschi
Frontiers Immunol. 5: 514, 2014

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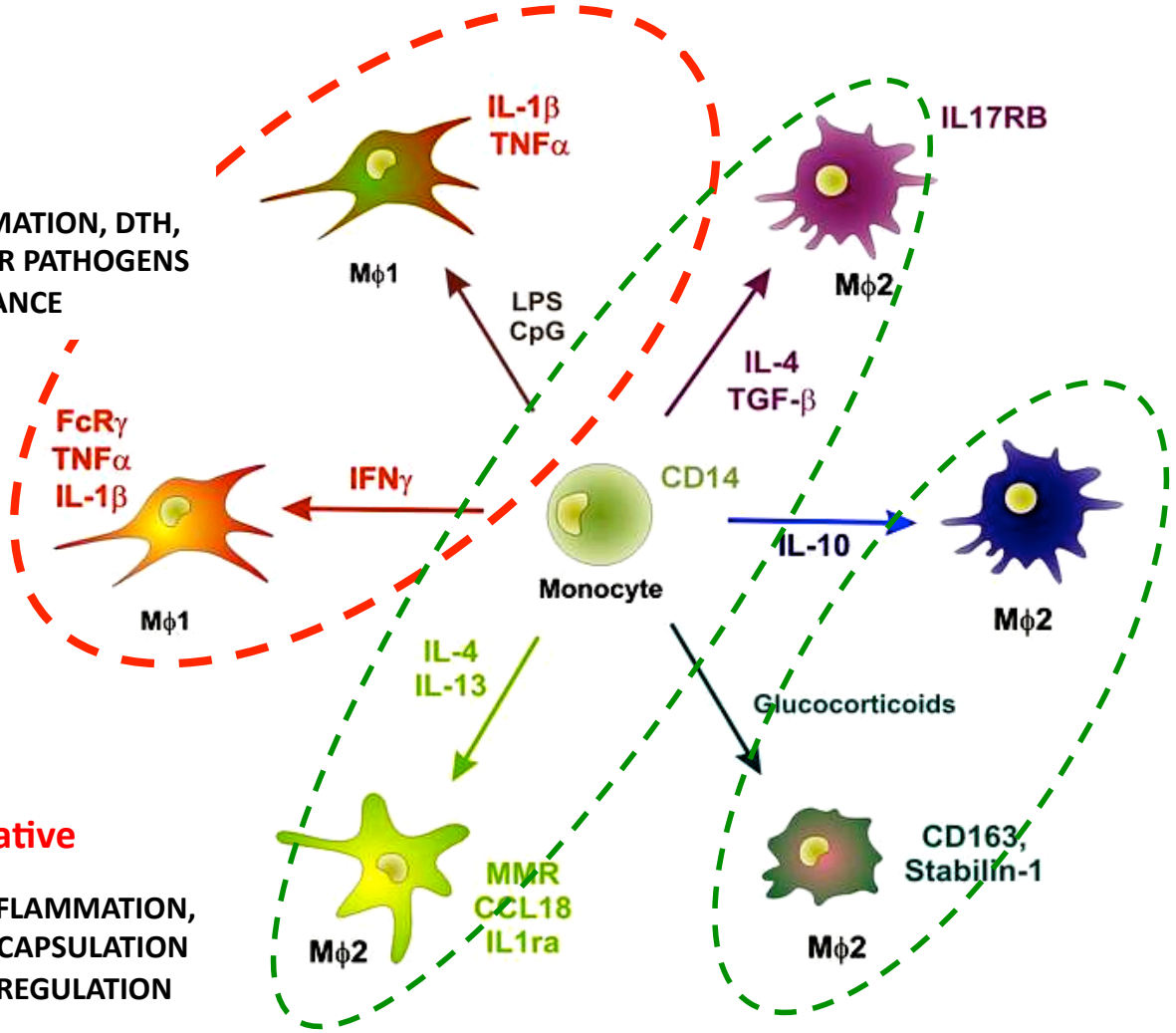
Heterogeneity of macrophage activation

M1
Classical

Th1 RESPONSES, INFLAMMATION, DTH, KILLING OF INTRACELLULAR PATHOGENS TUMOUR RESISTANCE



M2
Type II, Alternative

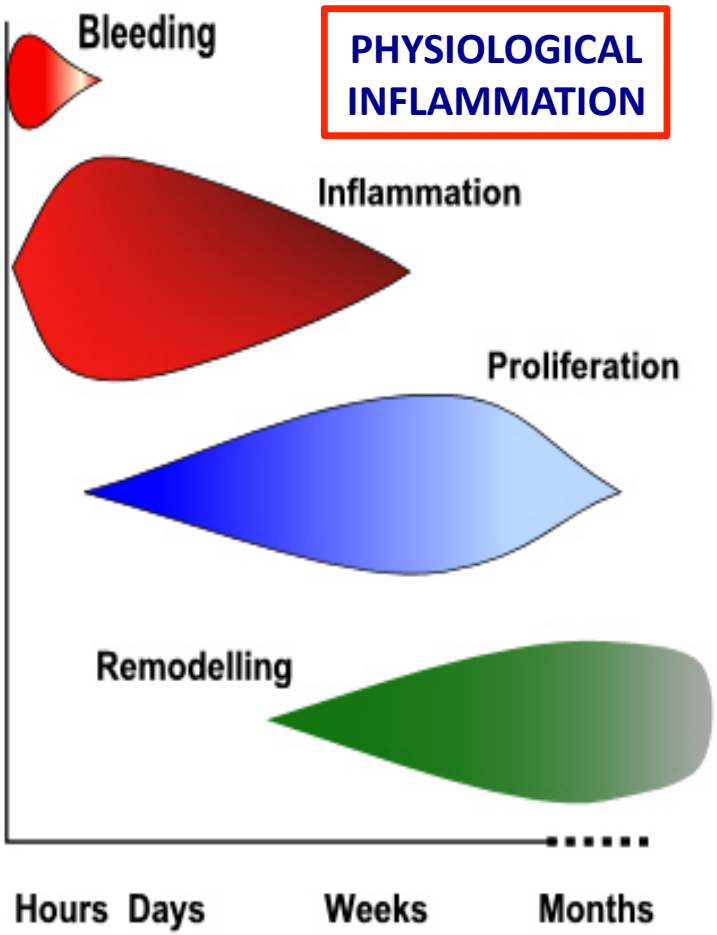
Th2 RESPONSES, TYPE II INFLAMMATION, ALLERGY, KILLING AND ENCAPSULATION OF PARASITES, IMMUNOREGULATION

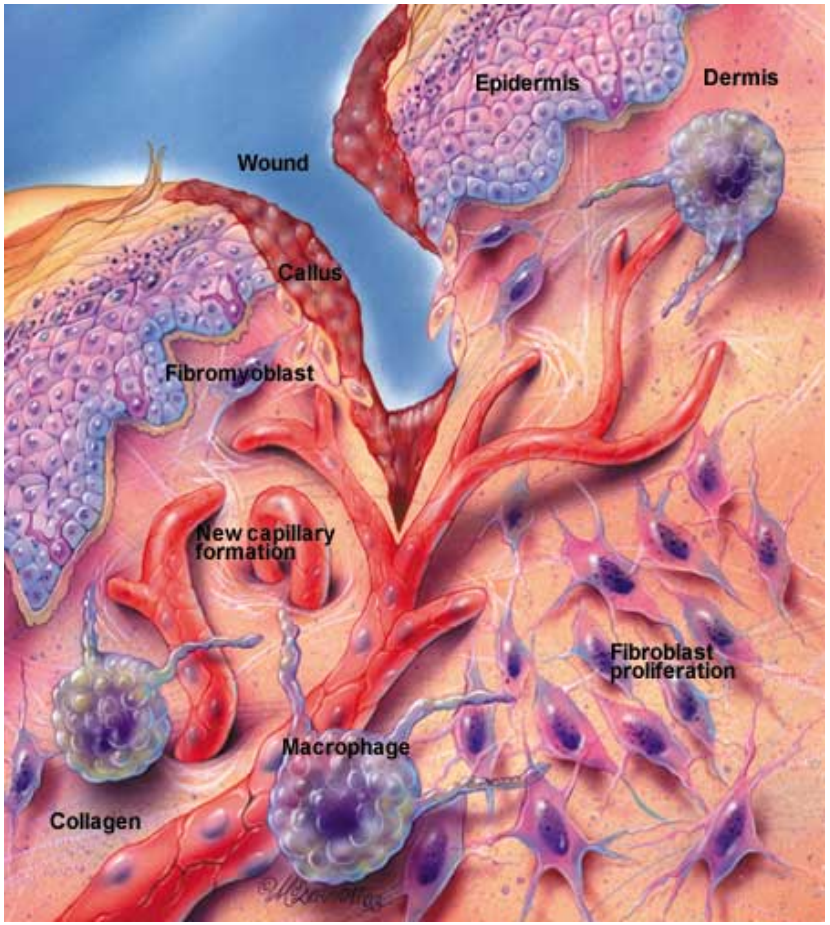
M2
Deactivated

IMMUNOREGULATION MATRIX DEPOSITION TISSUE REMODELLING

CONSIGLIO NAZIONALE DELLE RICERCHE

Macrophages and inflammation





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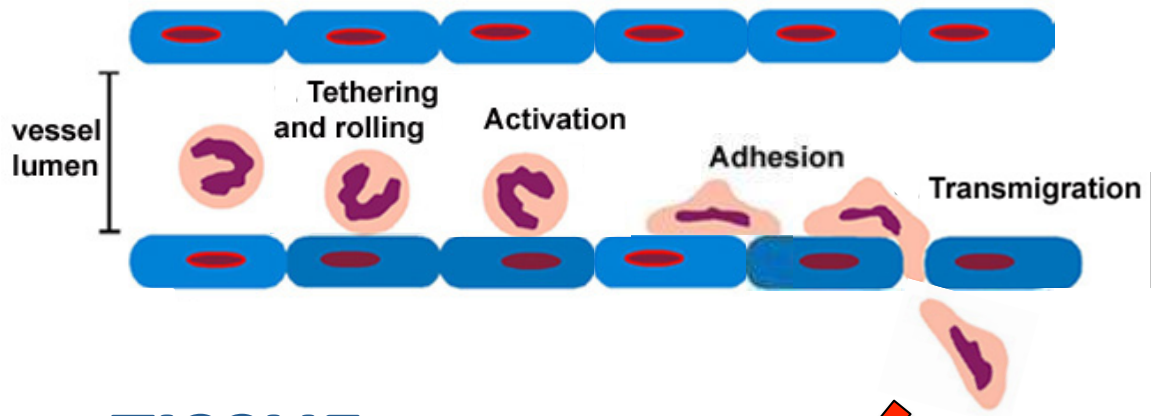
Monocytes/macrophages initiate the inflammatory process



TISSUE

Infection

Chemokines

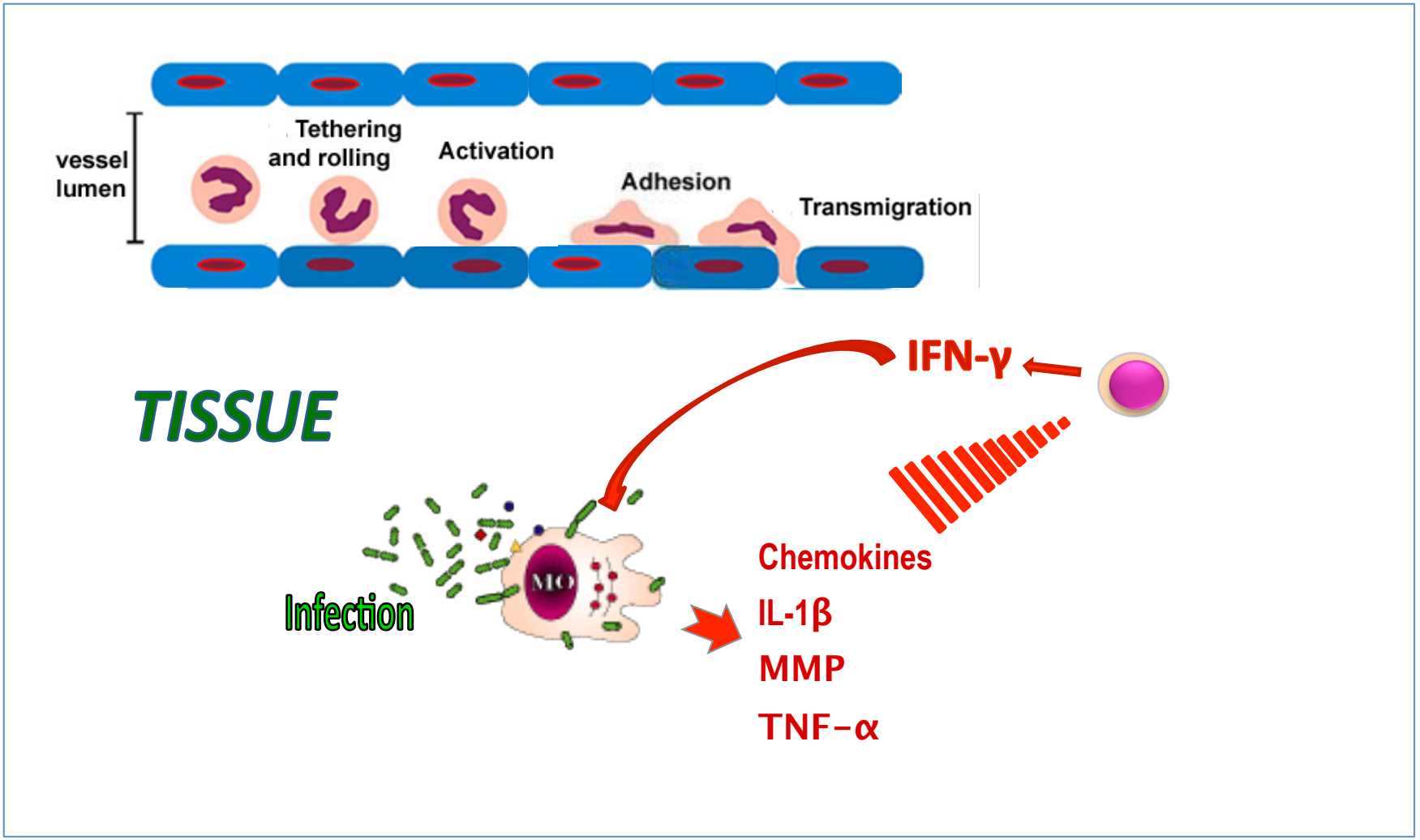
IL-1β

MMP

TNF-α

CONSIGLIO NAZIONALE DELLE RICERCHE

Monocytes/macrophages initiate the inflammatory process



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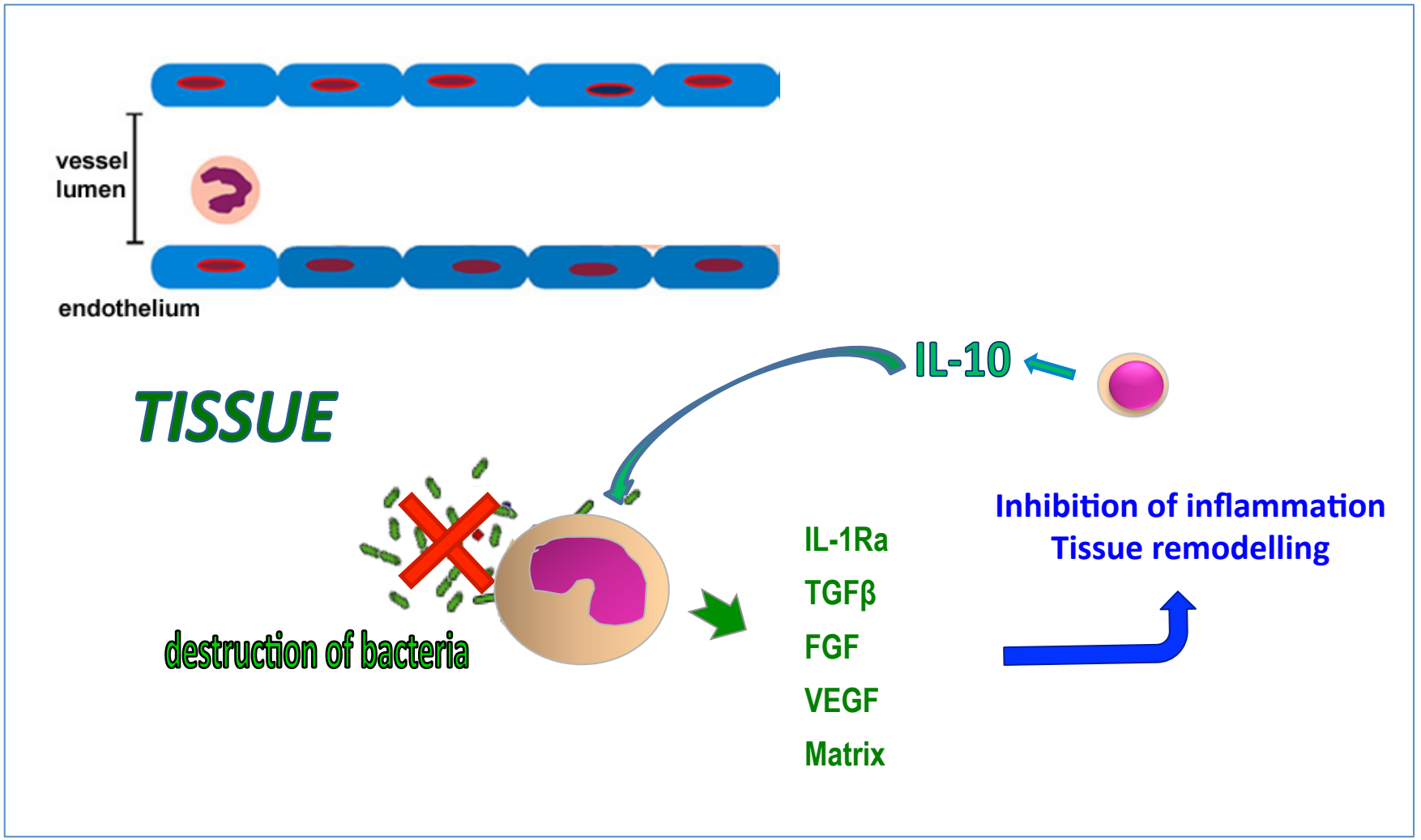
Macrophages contribute to resolving inflammation



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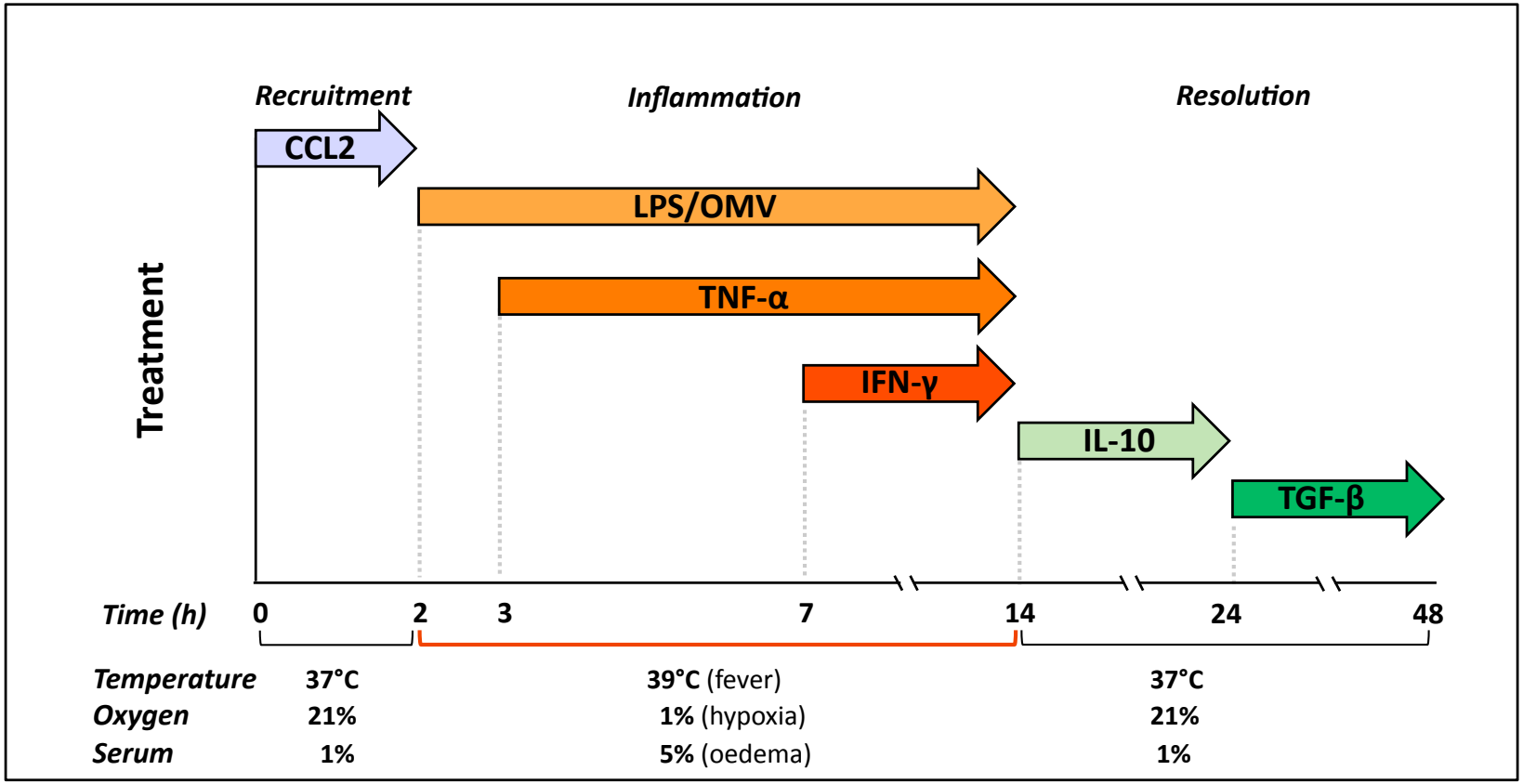
Kinetical monocyte-based model of human inflammation



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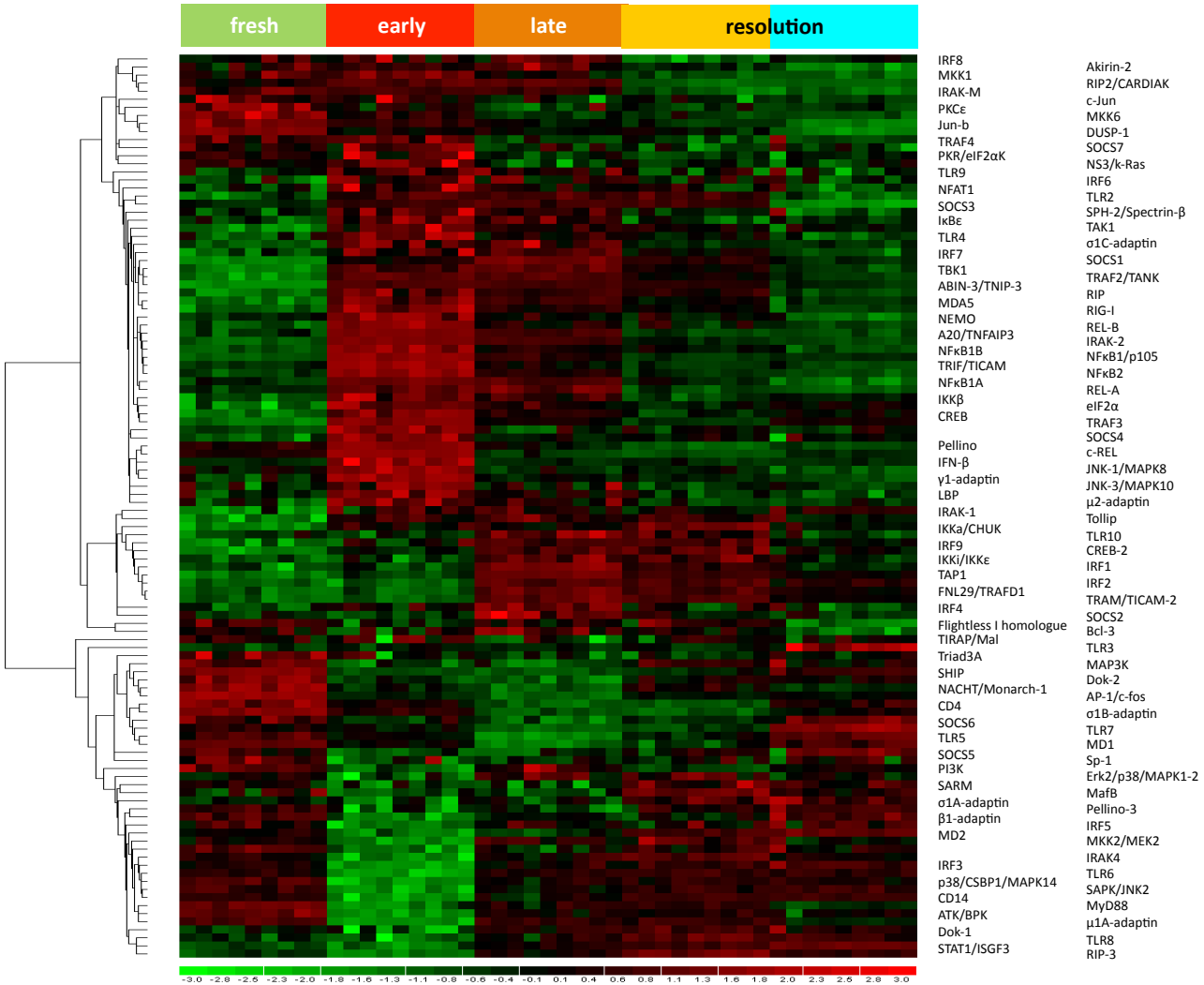
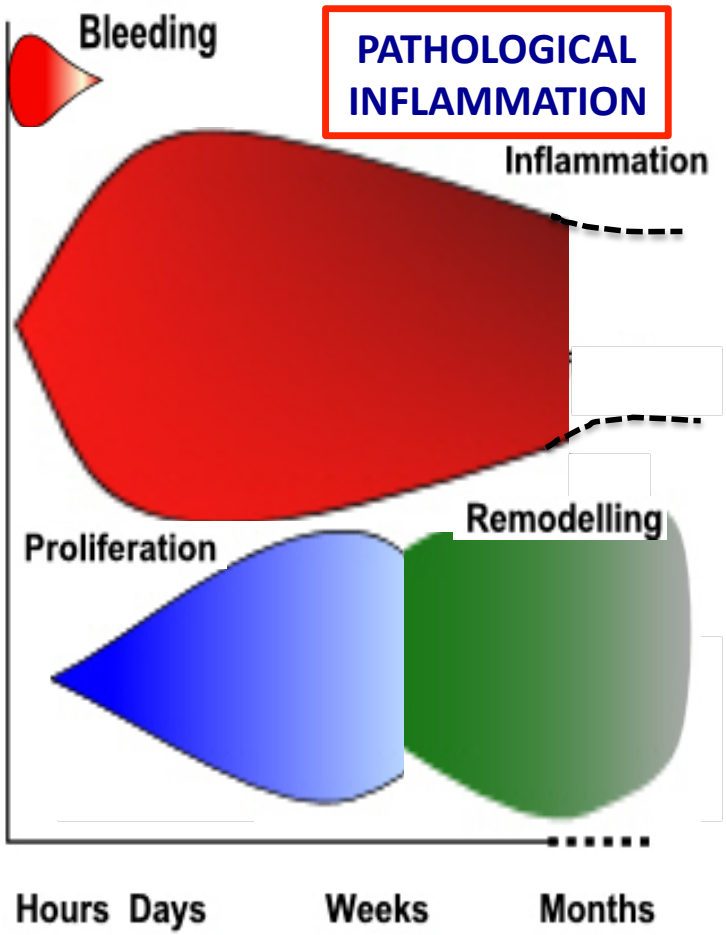
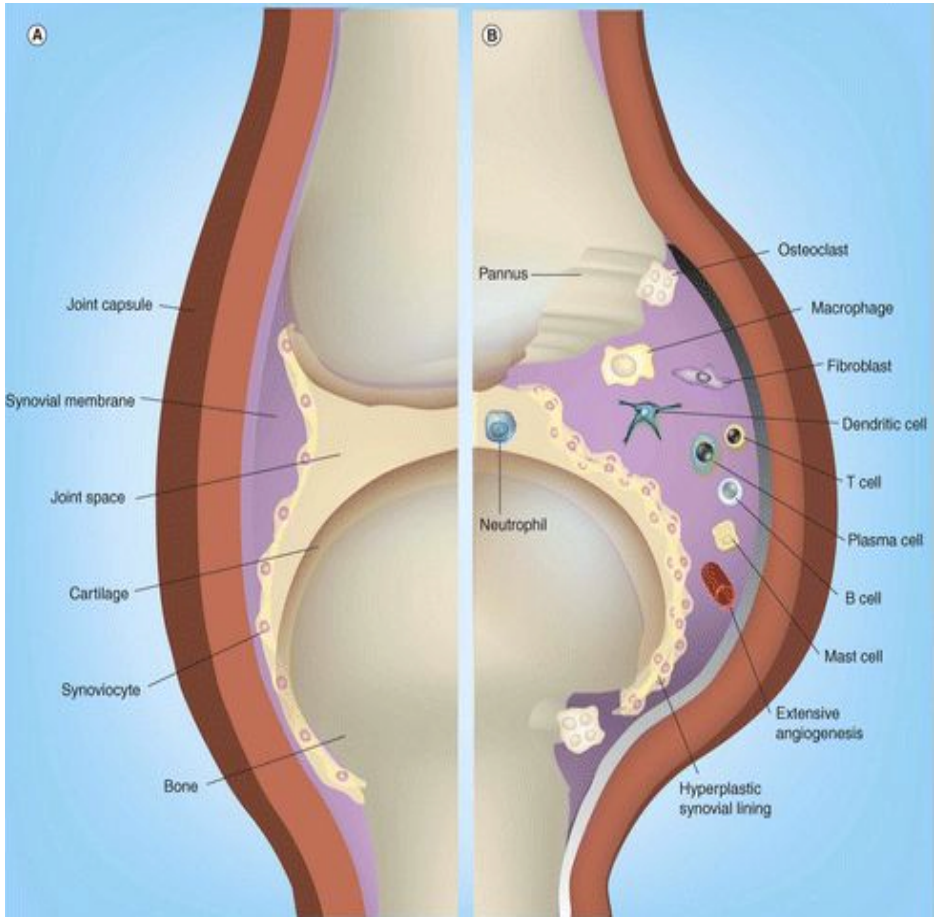
TLR and innate signalling genes



CONSIGLIO NAZIONALE DELLE RICERCHE

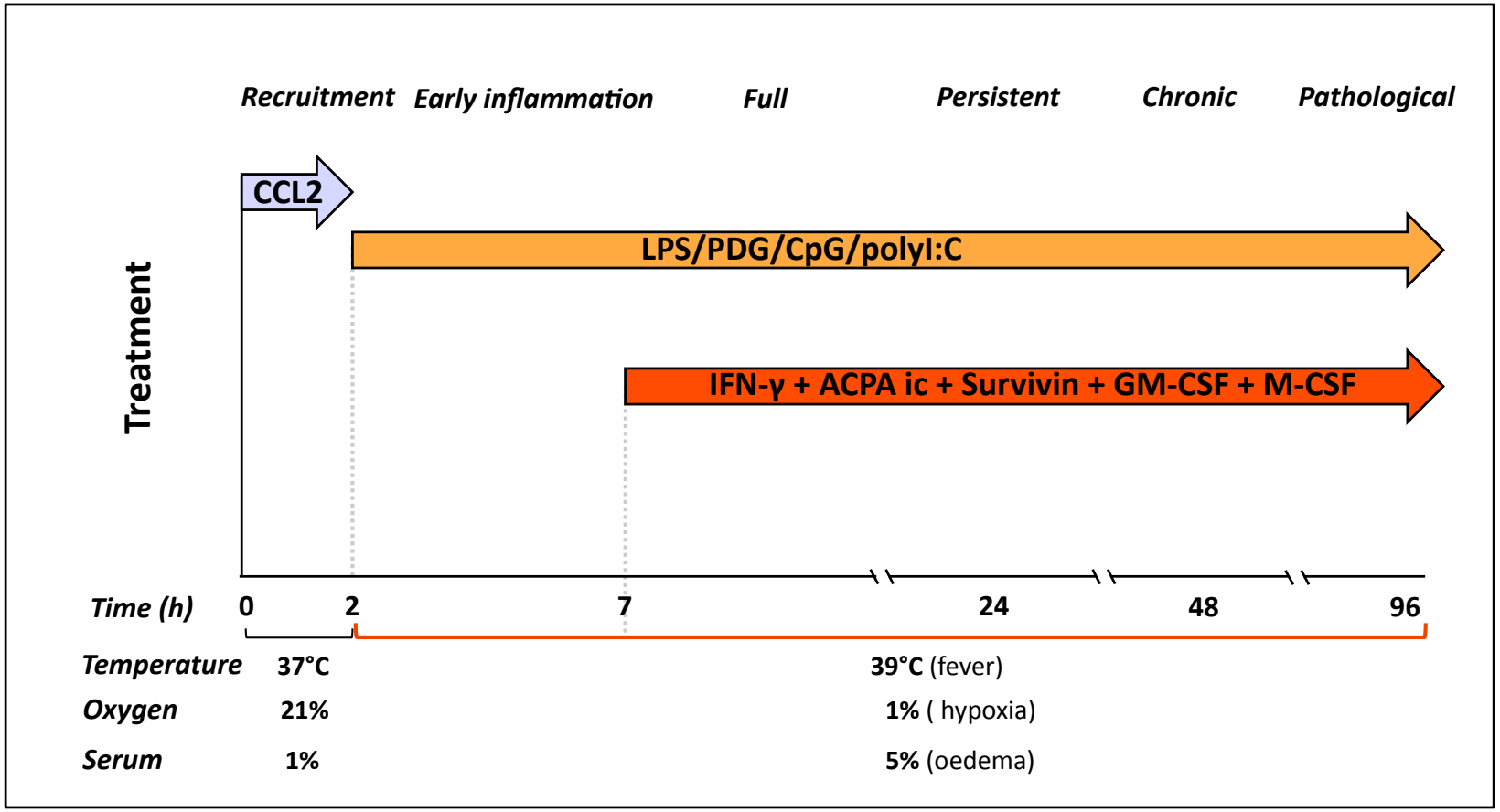
Macrophages and inflammation





CONSIGLIO NAZIONALE DELLE RICERCHE

Kinetical monocyte-based model of human pathological inflammation



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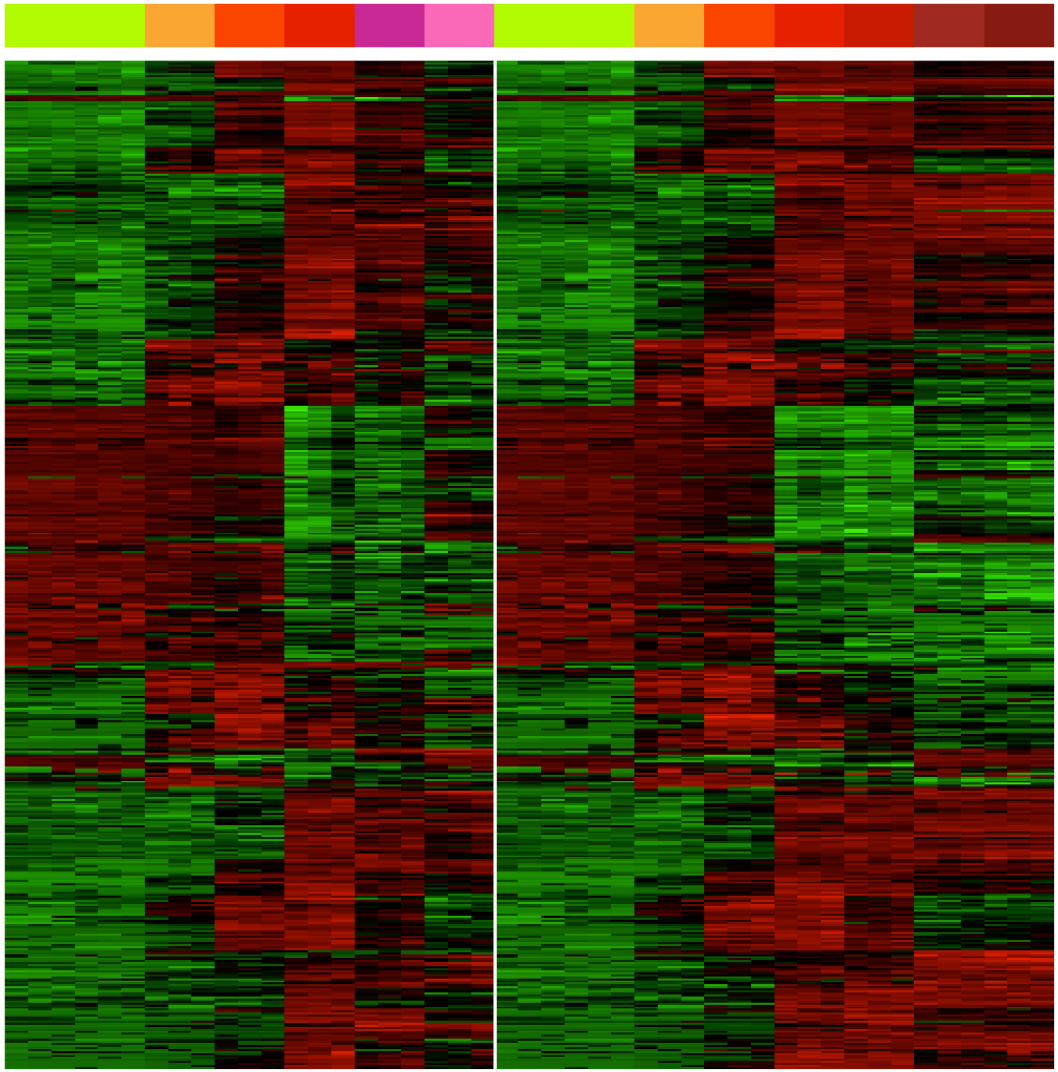
Gene expression patterns in resolving *vs*. chronic inflammation

resolving



chronic

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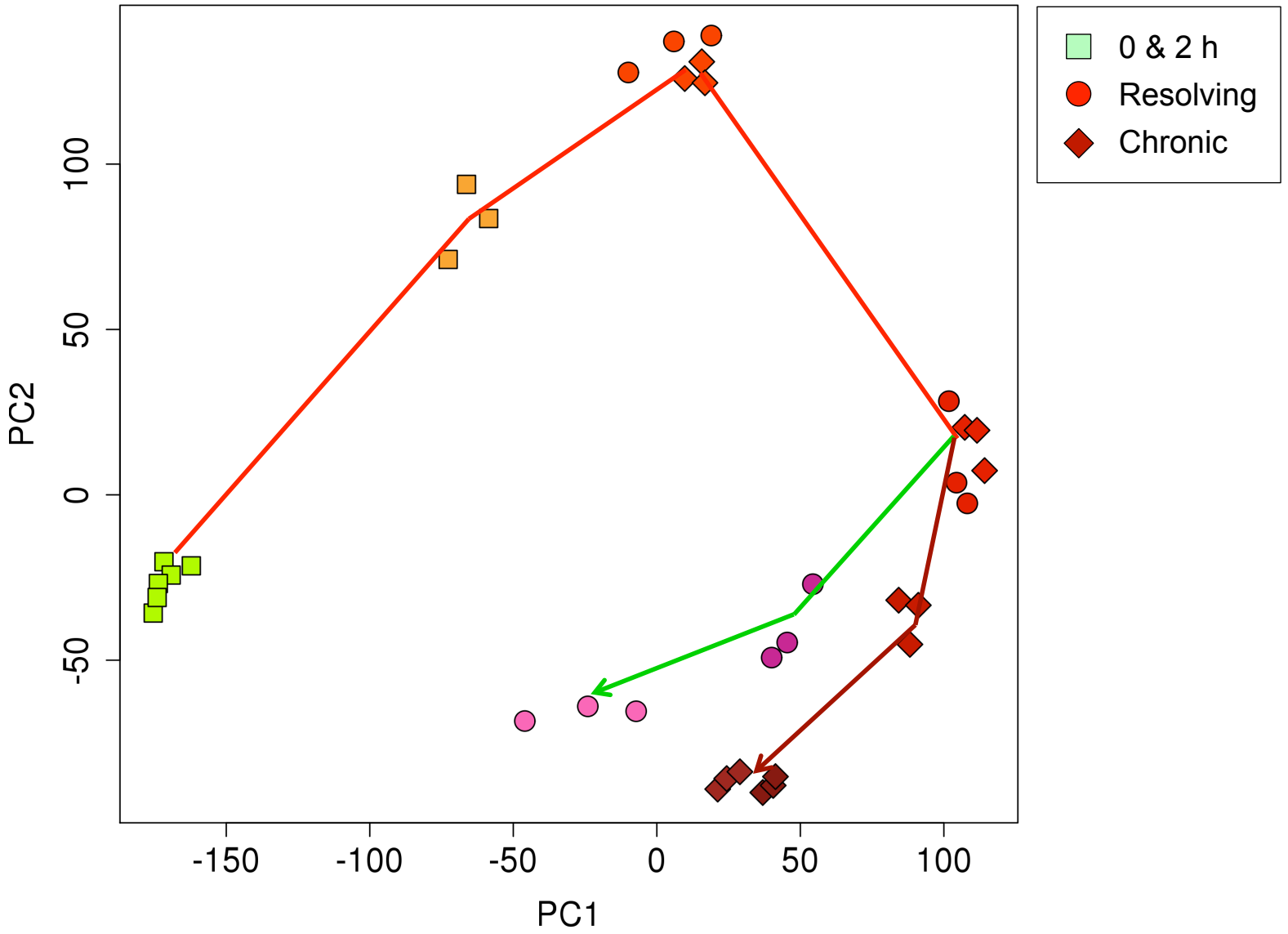
Principal component analysis



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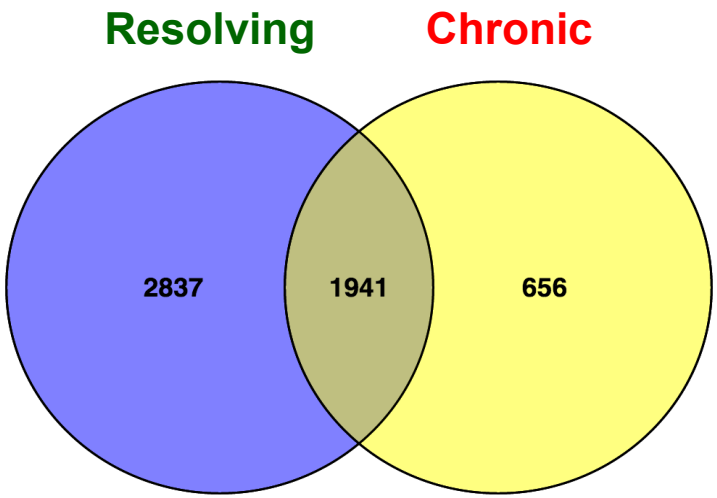
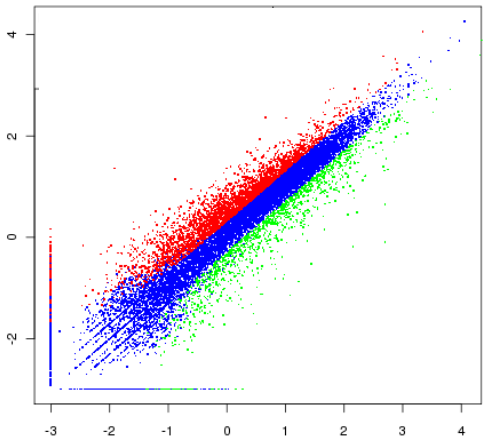
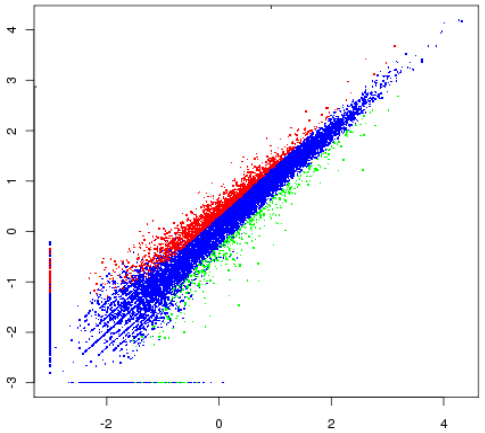
Differentially expressed genes



DEGs between 14 and 24 h

Resolving: 4778 DEGs





Chronic: 2597 DEGs

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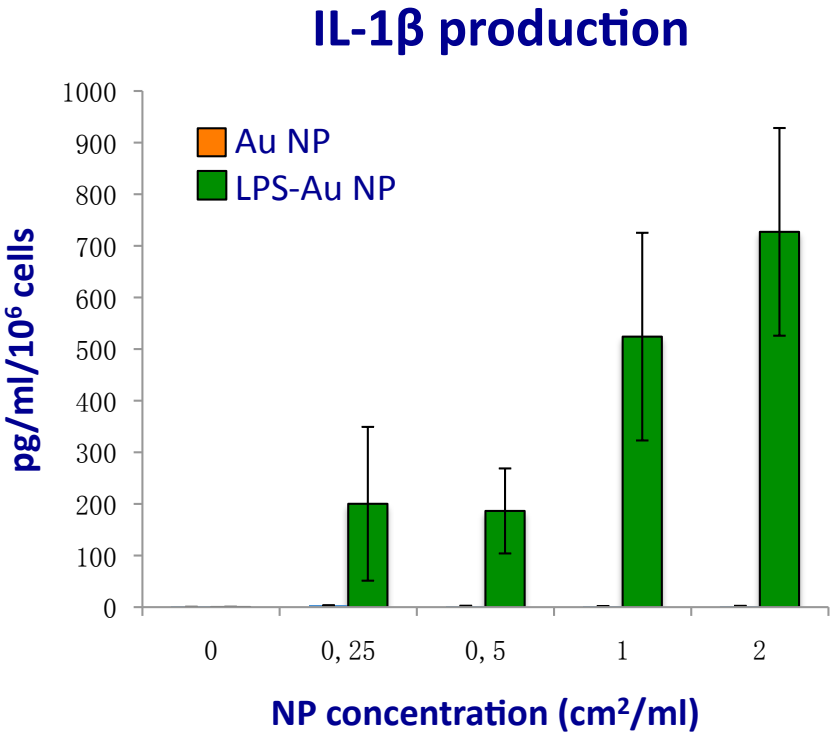
Do NPs induce inflammation?

The problem of endotoxin contamination



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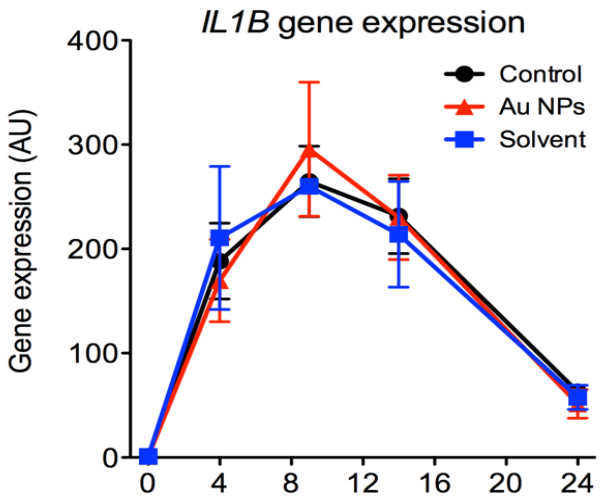
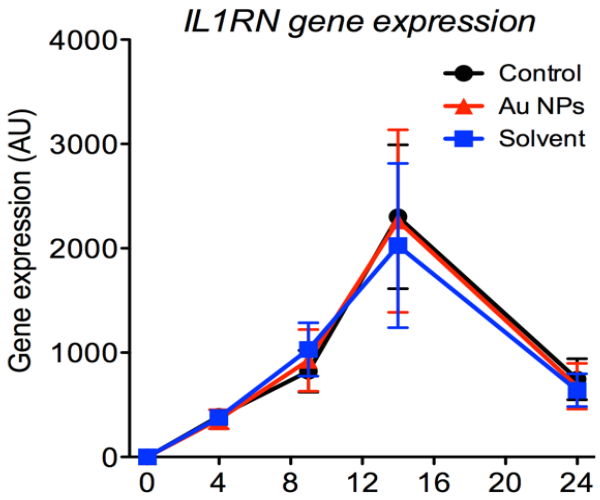
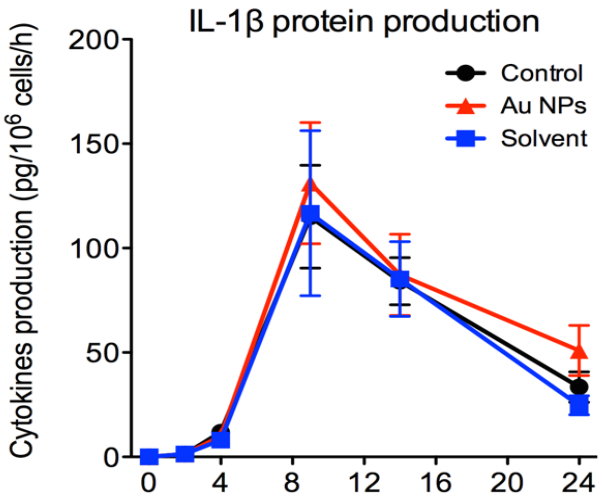
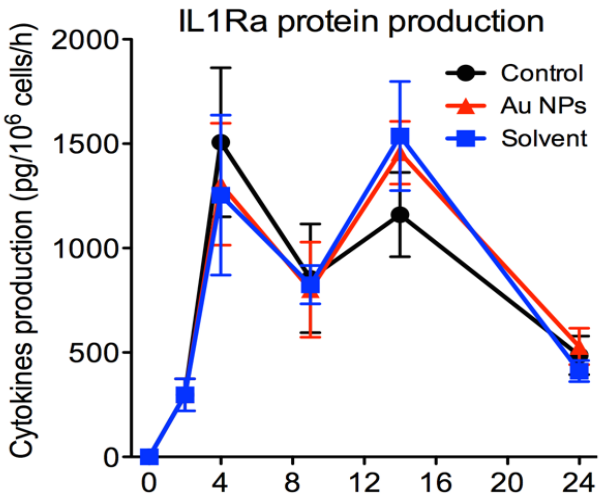
AuNP do not interfere with the course of a physiological inflammatory response









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Take home message

- For a good assessment of nano-effects on immune responses, you need **good models**
- **Human monocytes/macrophages** are a relevant model for assessing immunomodulatory and immunotoxic effects
- **Kinetic analysis** is important for discriminating between a physiological defence reaction and pre-pathological effects

CONSIGLIO NAZIONALE DELLE RICERCHE

There is at bottom only one genuinely scientific treatment for all diseases, and that is to **stimulate the phagocytes**

The Doctor's Dilemma, Act 1,
George Bernard Shaw (1906)

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ACKNOWLEDGEMENTS

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SEVENTH FRAMEWORK PROGRAMME

fondazione cariplo

Ministero dell'Istruzione dell'Università e Ricerca

HORIZON 2020